Pharmacokinetics of tezacaftor-ivacaftor (Symkevi) and elexacaftor-tezacaftor-ivacaftor (Kaftrio) treatment in children with Cystic Fibrosis

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52206

Source
ToetsingOnline

Brief title
SYM-CF

Condition

- Other condition
- Respiratory disorders congenital
- Congenital respiratory tract disorders

Synonym
cystic fibrosis

Health condition

cystische fibrose

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: (elexacaftor-)tezacaftor-ivacaftor, Children, Pharmacokinetics, Symkevi

Outcome measures

Primary outcome

The primary endpoint is to determine the exposure (area under the curve (AUC) and maximum plasma concentration (Cmax)) of elexacaftor, tezacaftor and ivacaftor.

Secondary outcome

1) To evaluate the relationship between covariates and PK parameters in order to explain inter-patient variability

2) To evaluate the relationship between AUC and through levels

3) To compare drug exposure in children of different age groups and compare with that in adults

4) To explore if there is a correlation between drug concentrations and clinical outcome measures (efficacy like exacerbation frequency, increase in weight, lung function parameters and safety like side effects.

Study description

Background summary

There are novel medicines in CF that target the CF transmembrane conductance regulator (CFTR) and increase its activity. These drugs improve the lung function, quality of life and body mass index in patients with specific mutations and might decrease pulmonary exacerbations. The combination of tezacaftor-ivacaftor (Symkevi®) is already being used by patients >= 12 years old and was approved by the European Medicine Agency (EMA) in September 2020 for children from the age of 6 years. The combination of elexacaftor-tezacaftor-ivacaftor (Kaftrio ®) will be available from January 2022 for patients >= 12 years old and was approved by the EMA in November 2021 for children from the age of 6 years. The clinical efficacy of these drugs is limited, some patients respond, while others do not or have side effects. The inter-individual variability (IIV) seems large and therefore this study hypothesizes that we might be over- or undertreating specific groups of patients, which can affect efficacy, side effects and costs of these expensive drugs. Very little is known about the pharmacokinetics (PK) of (elexacaftor-)tezacaftor-ivacaftor, especially in the paediatric population. Better knowledge of the PK may provide more insight into the exposure-response relationships and IIV.

Study objective

This study aims to evaluate the PK profile and IIV of drug exposure in plasma in children (aged 6-17 years) receiving (elexacaftor-)tezacaftor-ivacaftor. Secondary objectives are to evaluate the relationship between covariates and PK parameters that explain the IIV, to compare drug exposure in children with that in adult, and to explore the correlation between drug concentrations and clinical outcome parameters.

Study design

National multi-center, observational with interventional sampling, pharmacokinetic study.

Study burden and risks

During the regular visits to the hospital (every three months) blood samples are taken for clinical routine purposes. For this study a small extra volume (1 ml) will be obtained when the regular sample is taken. Children will not receive extra venapunctures for this study. In addition to the blood obtained by venapuncture, dried blood spot (DBS) samples will be collected. One full curve of 3 time points (t=0, t=4 and t=8) will be collected at home after DBS instruction during the year visit, and will be sent to the hospital. If during a regular visit no venous blood sample is taken for routine care, a DBS sample will be taken at a random time point. Furthermore, leftover material from blood samples taken during routine patient care will be collected as well. Patients will be followed during a maximum of 12 months (4-5 visits) per intervention

(Symkevi and/or Kaftrio). If patients already participated in the trial during Symkevi treatment, new informed consent will be asked for another follow-up period during Kaftrio treatment.
The patient will not have direct benefit from participation in this study. We aim for improved treatment of CF patients and in that respect the results of the study may improve treatment in the future for the patients participating in the study or any patient with similar characteristics.
Clinical data regarding the pharmacokinetics in children are limited. Better knowledge of the PK may provide more insight into the exposure-response relationships and its inter-patient variability. This knowledge may result in more insight in the efficacy of the drugs and contribute to the possible development of individualized dosing schemes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Use a combination therapy of (elexacaftor-)tezacaftor-ivacaftor for a minimum period of 8 days in regular care or compassionate use
- CF patients aged 6 years and older
- Signed informed consent from the patient when >=16 years, from the patient and both parents for patients aged 12-15 years, from both parents aged 6-11 years

Exclusion criteria

- History of poor compliance deemed by the physician
- Concomitant use of drugs that have an inhibitory or inducing effect on the CYP3A4 enzyme metabolism 14 days before the blood collection, if the patient uses one or more of these medicines the blood collection of the upcoming visit will be skipped:
o Inducers of CYP3A: rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John*s wort
o Inhibitors of CYP3A: ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin, fluconazole, erythromycin and grapefruit juice

- Patient or parent refusal

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2021
Enrollment:	30

Type:	Anticipated

Ethics review

Approved WMO Date:	30-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL75811.018.21